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Friedreich Ataxia in Acadian Families From Eastern Canada: Clinical Diversity With Conserved Haplotypes

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The gene for Friedreich ataxia (FRDA), an autosomal-recessive neurodegenerative disease, remains elusive. The current candidate region of about 150 kb lies between loci FR2 and F8101 near the D9S15/D9S5 linkage group at 9q13–21.1. Linkage homogeneity between classical FRDA and a milder, slowly progressive Acadian variant (FRDA-Acad) has been demonstrated. An extended D9S15–D9S5 haplotype (C6) predominates in FRDA-Acad chromosomes from Louisiana. We studied 10 Acadian families from New Brunswick, Canada. In eight families, affected individuals conformed to the clinical description of FRDA-Acad; in one, 2 sibs presented with spastic ataxia (SPA-Acad). In the last family, 2 sibs had FRDA-Acad, and one had SPA-Acad. We found that SPA-Acad is linked to the FRDA gene region. The C6 haplotype and a second major haplotype (B7) were identified. The same ataxia-linked haplotypes segregated with both FRDA-Acad and SPA-Acad in two unrelated families. The parental origins of these haplotypes were different. Our observation of different phenotypes associated with the same combination of haplotypes may point to the influence of the parent of origin on gene expression, indicate the effect of modifier genes, or reflect the presence of different mutations on the same haplotype. Our findings underline the need to investigate families with autosomal-recessive ataxias for linkage to the FRDA region, despite lack of key diagnostic manifestations such as cardiomyopathy or absent deep-tendon reflexes. © 1996 Wiley-Liss, Inc.

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INTRODUCTION

Acadian Friedreich ataxia (FRDA-Acad) is an early-onset, progressive, neurodegenerative disorder characterized by gait ataxia, muscle weakness, loss of deep-tendon reflexes in the lower limbs, dysarthria, and sensory disturbances [Barbeau et al., 1984]. It has autosomal-recessive inheritance. FRDA-Acad and the more severe classical form of FRDA (non-Acadian) [Geoffroy et al., 1976] display the same neurologic symptoms and ages of onset. The progression of disease is slower in FRDA-Acad. Hypertrophic cardiomyopathy and abnormal glucose metabolism have not been reported in FRDA-Acad.

Cases of FRDA-Acad were described in Acadian families from Louisiana and Eastern Canada [Barbeau et al., 1984]. The common roots of these populations reach back to Acadia, a French colony founded in 1605 in the area that later became Nova Scotia and New Brunswick. By 1755 most Acadians were deported or had left the region voluntarily as a result of the Treaty of Utrecht (1713) when Acadia was yielded to England. Many Acadians settled in Louisiana, while others returned to the Atlantic provinces of Canada after some years in exile [Arseneault, 1978].

Tight linkage of the gene responsible for FRDA-Acad was shown to D9S15 and D9S5 in Louisiana Acadians [Chamberlain et al., 1989; Keats et al., 1989]. These loci on proximal 9q are in tight linkage with classical FRDA [Chamberlain et al., 1988; Fujita et al., 1989]. Linkage homogeneity of clinically distinct diseases suggests that different mutations affect the same gene or may point to different but very closely spaced and functionally homologous genes.

FRDA-Acad in the Louisiana population is associated with a specific D9S15–D9S5 haplotype (C6) [Sirugo et al., 1992]. The C6 haplotype is rare in classical FRDA [Richter et al., 1992].

Here we detail clinical findings, linkage, and haplotype analysis of the FRDA gene region in 10 families. A

preliminary report on the linkage study of some of these families has appeared [Richter et al., 1991].

MATERIALS AND METHODS

Family Material, Neurologic Examination, and Sample Collection

We visited 10 families (Figs. 1, 2) with 23 affected individuals living in the Acadian peninsula of New Brunswick, an area of roughly 10,000 km^2, corresponding to <0.1% of the area of Canada. Families 904–908 and 910 were part of the original description of FRDA-Acad [Barbeau et al., 1984].

After informed consent complying with institutional and national standards [Knoppers and Laberge, 1991], we collected blood for DNA extraction and establishment of lymphoblastoid cell lines from 18 affected individuals and 140 other relatives. We discovered two historic marriage loops between members of three ataxia families (Fig. 1).

Basic neurologic examinations were conducted in the field on all sampled individuals by two of us (J.-P.B. and S.B.M.). In addition, nerve conduction velocities were determined in patients G.H. and C.H. (Fig. 1, individuals IV-2 and IV-3).

DNA Extraction and Polymorphisms in the FRDA Region

DNA was extracted using standard procedures from 10 ml of venous blood collected in EDTA tubes. Map order of the polymorphic loci used in this study is shown in Figure 3 [Carvajal et al., 1995; Montermini et al., 1995].

RFLP analysis for the following polymorphisms, two-allele *Msp*I (probe MCT112) at D9S15, two-allele *Taq*I (probe DR47) at D9S5, and three-allele *Bst*XI (probe 26P) at D9S5, was performed as previously described [Chamberlain et al., 1988, 1989; Fujita et al., 1989, 1990]. The D9S15 (MCT112-MS) microsatellite polymorphism can be revealed by two different oligonucleotide pairs [Wallis et al., 1990; Fujita et al., 1990]. We used the method of Wallis et al. [1990]. However, duplicate control samples were also analyzed using the MCT-MS oligonucleotides described in Fujita et al. [1990]. The resulting allele numbering system was identical to that of Sirugo et al. [1992] in studies of the Louisiana Acadians. The microsatellite polymorphisms at GS4 (D9S110), GS2 (D9S111) [Sirugo et al., 1992], FR1 (D9S202), FR7 (D9S887), and FR5 (D9S889) were assayed as described [Rodius et al., 1994]. In families 903, 907, and 909, additional microsatellite polymorphisms at FR2 (D9S886) and FR8 (D9S888) and the single-strand conformational polymorphism (SSCP), corresponding to A3U1 [Montermini et al., 1995], were studied. The CD1 SSCP on fragments generated by oligonucleotides in exon 7 of the STM-7 gene [Carvajal et al., 1995] and CS2, a two-allele *Aci*I RFLP [Montermini et al., 1995], were investigated in family 907, while the microsatellite polymorphisms F71 and F5225 [Montermini et al., 1995] were studied only in families 903 and 909.

Investigation of Possible Doubtful Paternity in Family 906

Possible paternity problems, suggested by the differences in the disease course between patients IV-2–IV-4, were ruled out prior to detailed analysis of the FRDA region. We used VNTR marker DXS52 (Xq26–28) [Richards et al., 1991], dinucleotide repeat markers PAX3 (2q35–37) [Wilcox et al., 1992], D5S204 (5q11.2–13.3) [Mankoo et al., 1990], and D5S351 (5q11.2–13.3) [Hudson et al., 1992], and two polymorphic regions in CFTR, an AT repeat in intron 17b [Zielenski et al., 1991], and a CA repeat in intron 8 [Morral et al., 1991]. No inconsistencies were observed.

Linkage and Extended Haplotype Analysis in the FRDA Region

Linkage between D9S15 (MCT112/*Msp*I), D9S5 (26P/*Bst*XI, DR47/*Taq*I), and the two forms of ataxia

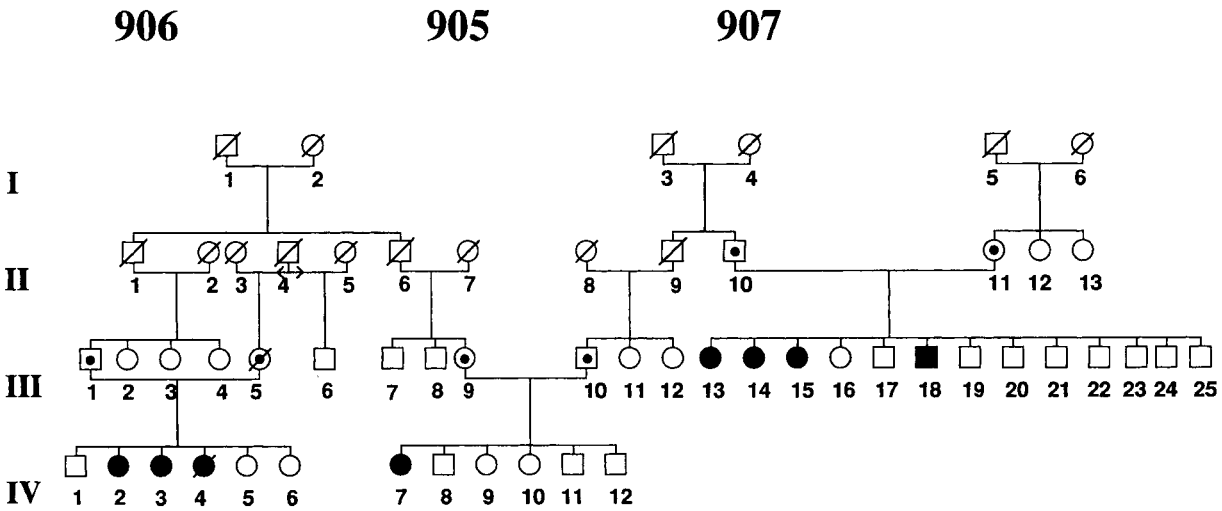


Fig. 1. Acadian ataxia families from New Brunswick with historical marriage loops. All living individuals were sampled for DNA. Square, male; circle, female; dot, obligate ataxia carrier; solid symbol, affected individual; slash, deceased individual.

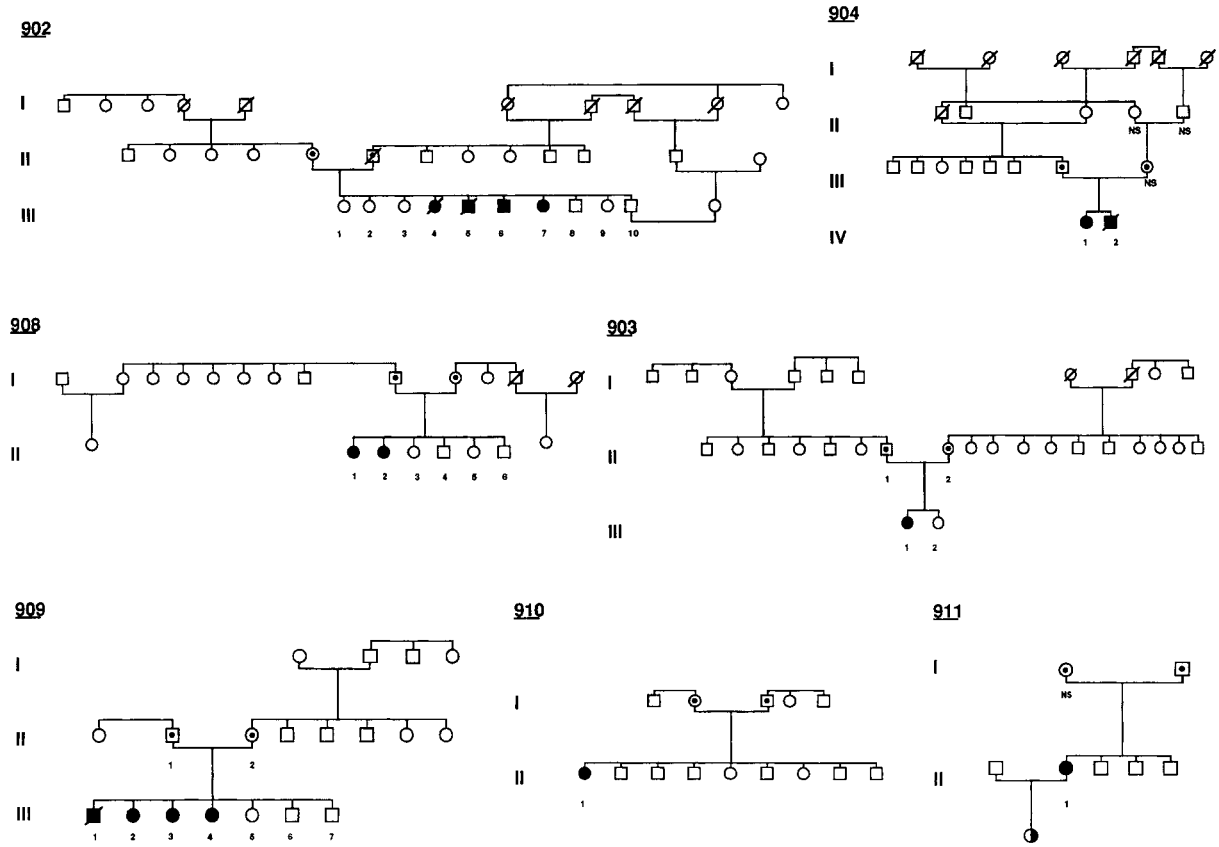


Fig. 2. Acadian ataxia families included in study. Symbols as in Figure 1. ns, not sampled.

was tested using the LINKAGE package, version 5.1 [Lathrop and Lalouel, 1988]. We assumed that recessive ataxia allele frequency was 0.0045.

We constructed extended haplotypes for ataxia and normal chromosomes from typings obtained on the obligate heterozygote parents. They are composed of nine polymorphic markers (GS4, MCT112-MS, MCT112/*Msp*I, GS2, 26P/*Bst*XI, DR47/*Taq*I, FR1, FR7, and FR5). Marker order was derived from long-range mapping studies [Wilkes et al., 1991; Fujita et al., 1991; Rodius

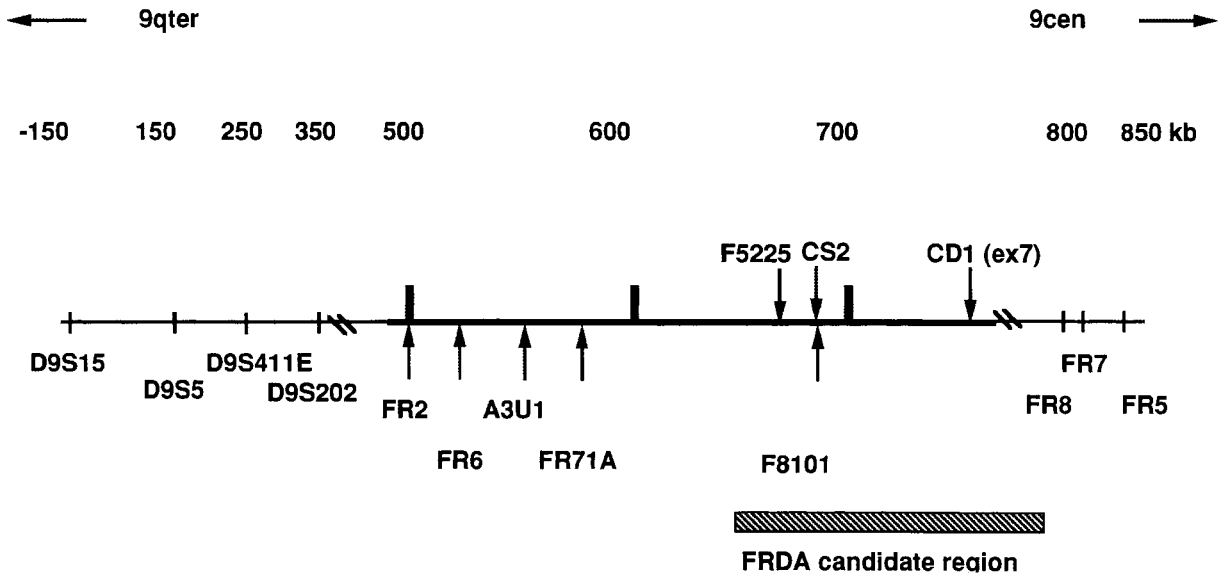


Fig. 3. Polymorphic loci on 9q in the FRDA region.

et al., 1994]. Core haplotypes, composed of GS4, MCT-MS, GS2, and 26P (*Bst*X1), were designated as in Sirugo et al. [1992]. Haplotypes distinct from A–to F [Sirugo et al., 1992] are identified with letters starting at Q.

RESULTS

Clinical Investigation

Clinical manifestations in affected individuals are shown in Table I, in order of decreasing severity. All parents were found to be neurologically normal. Patients from 8 of the 10 families conformed to the clinical criteria of FRDA-Acad [Barbeau et al., 1984]. In family 909 we identified 3 sibs with slowly progressive ataxia with preserved or increased deep-tendon reflexes and lower-limb spasticity. This clinical picture is uncommon for FRDA-Acad. In family 906, 2 sibs (C.H. and R.H.) have typical FRDA-Acad, while their sister G.H. has increased deep-tendon reflexes. False paternity has been ruled out, using highly polymorphic markers on chromosomes X, 2, 5, and 7 (results not shown).

Linkage Analysis of FRDA-Acad and Spastic Ataxia-Acad (SPA-Acad)

The similar clinical manifestations of FRDA-Acad in New Brunswick and Louisiana Acadians and the common historical origins of the two populations prompted us to presuppose linkage of FRDA-Acad in New Brunswick Acadians to loci on 9q13–21.1. For the linkage study we assumed no recombination between markers, linkage equilibrium, and equal male and female recombination rates. We obtained a LOD score of 3.67 (θ = 0.00) between FRDA-Acad and the D9S15–D9S5 linkage group. When the known linkage disequilibrium between FRDA and the FRDA haplotypes was taken into account, we obtained a LOD score of 5.21 (θ = 0.00). These results show strong evidence of linkage of FRDA-Acad to the D9S15–D9S5 linkage group in the New Brunswick population. There were no recombinants between markers at D9S15, D9S5, and FRDA-Acad.

We tested the hypothesis of linkage of SPA-Acad found in two families to D9S15–D9S5. Especially interesting was the extended kindred made up of families 905–907, with both FRDA-Acad and SPA-Acad phenotypes segregating (Fig. 1). For the analysis we assumed that all affected individuals in the study had the same disease phenotype. Assuming linkage equilibrium, we obtained a LOD score of 6.87 (θ = 0.00) between the disease(s) and D9S15–D9S5. The use of haplotypes in linkage disequilibrium increased the LOD to 8.97 (θ = 0.00). No recombinants were detected between the markers used and SPA-Acad.

These results indicated that FRDA-Acad and SPA-Acad were likely in the same allelic series.

Haplotype Analysis in FRDA-Acad and SPA-Acad in a 1-megabase Region Encompassing the FRDA Locus

In Table II we present haplotypes composed of nine polymorphisms in the FRDA region on ataxia-associated chromosomes. The results are in order of decreasing

TABLE I. Clinical Manifestations of Acadian Ataxia Patients*

Family	902		903	904	908		910	911	907			905	906			909		
Individual	A.L.	D.L.	D.D.	M.T.	I.L.	N.L.	E.N.	B.W.	F.R.	A.D.R.	A.N.R.	E.R.	G.R.	G.H.	C.H.	R.H.	B.N.	A.N.	M.N.
No. in figure 1	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
No. in figure 2	III-6	III-7	III-1	IV-1	II-1	II-2	II-1	II-1	III-13	III-14	III-18	III-15	IV-7	IV-2	IV-3	IV-4	III-2	III-3	III-4
Sex	M	F	F	F	F	F	F	F	F	F	M	F	F	F	F	F	F	F	F
Age at examination	49	41	24	29	37	31	46	32	49	48	38	36	42	37	38	32†	26	25	23
Age at onset	12	11	11	14	11	11	12	10	14	14	18	17	13	12	17	14	16	15	12
Wheelchair-bound	39	26	21	22	27	±	31	±	36	37	±	0	30	0	±	17	0	0	0
Ataxia of gait	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	±	±
Progression, last 2 years	+	+	+	+	+	+	+	+	±	±	±	±	±	±	+	?	0	+	+
Dysarthria	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+
Muscle weakness	+	+	+	+	+	+	+	+	0	0	0	0	+	0	0	?	0	0	0
Vibratory sense	0	0	↓+	0	0	↓+	↓+	↓+	↓+	↓+	↓+	↓+	0	↓+	↓+	↓+	↓+	↓+	↓+
Deep-tendon reflexes	0	0	0	0	0	0	0	0	0	0	0	0	0	↑+	0	0	+	↑+	↑+
Babinski sign	0	+	+	+	+	+	+	+	+	+	+	±	+	±	0	±	0	±	+
Pes cavus	+	+	0	+	+	+	+	±	0	0	0	0	+	+	0	+	–	–	±
Scoliosis >10°	+	+	±	±	+	±	+	0	?	?	±	±	+	+	+	?	0	0	0
Incontinence	+	+	+	0	0	+	+	+	+	+	0	0	+	+	0	?	0	0	+

*+, presence of manifestation; ±, ambiguous manifestation; 0, absence of manifestation; ?, not reported; ↑, increased; ↓, decreased; †, deceased; na, not applicable.

clinical severity, as in Table I. Since some of the families form extended kindreds, we specify the parental origin of each haplotype. For the same reason we have not attempted to determine the number of independent ataxia chromosomes that segregate in the population.

Among five extended haplotypes seen, two predominate, i.e., C6 and B7 [Sirugo et al., 1992]. C6, the major ataxia-associated haplotype in Louisiana Acadians, is present eight times, while haplotype B7 is observed six times. This haplotype is identical at all loci to a minor haplotype associated both with classical FRDA in Quebec and with FRDA-Acad in Louisiana.

Haplotype B9, found in family 907, is identical at all loci tested to the predominant haplotype associated with the classical form of FRDA in the province of Quebec (Richter et al., in preparation). We observed the unique haplotype Q6 in a homozygous individual (family 911). The two copies are likely identical by descent.

The R13 haplotype in family 906 is also unique, and is associated with both FRDA-Acad and SPA-Acad. The patients are homozygous for R13, while in their paternal second cousin (affected individual G.R. in family 905) the combination of this haplotype with C6 manifests clinically as FRDA-Acad.

In family 909 the combination of C6 and B7 haplotypes manifests clinically as SPA-Acad, while in family 903 the same combination is associated with FRDA-Acad. We note that the parental origin of the haplotypes is reversed in the two families. Additional studies with polymorphisms at FR2, A3U1, FR71A, F5225, and FR8 failed to reveal differences between the B7 and C6 haplotypes seen in these families (Table III).

We observed 19 different haplotypes on normal chromosomes (Table II). In family 904 we were unable to deduce the normal maternal chromosome from the unaffected children due to the absence of a sample from the mother.

TABLE II. Extended FRDA and Normal Haplotypes Identified in Acadian Ataxia Families*

Locus	D9S110	D9S15	D9S15	D9S111	D9S5	D9S5	D9S202			
Polymorphism	GS4	MCT-MS	MCT-MspI	GS2	26P	DR47	FR1	FR7	FR5	Core haplotype
Family/origin										
FRDA										
902/p	6	2	2	2	3	2	4	2	8	C6
902/m	6	2	2	2	3	2	4	2	8	C6
903/p	6	2	2	2	3	2	4	2	8	C6
903/m	7	2	2	2	2	2	2	7	7	B7
904/p	6	2	2	2	3	2	4	2	8	C6
904/m	6	2	2	2	3	2	4	2	8	C6
908/p	7	2	2	2	2	2	2	7	7	B7
908/m	7	2	2	2	2	2	2	7	7	B7
910/p	7	2	2	2	2	2	2	7	7	B7
910/m	7	2	2	2	2	2	2	7	7	B7
911/p	6	4	1	5	1	2	2	3	8	Q6
911/m	6	4	1	5	1	2	2	3	8	Q6
907/p	6	2	2	2	3	2	4	2	8	C6
907/m	9	2	2	2	2	2	2	6	7	B9
905/p	6	2	2	2	3	2	4	2	8	C6
905/m	13	4	1	5	3	1	4	9	4	R13
906/p	13	4	1	5	3	1	4	9	6	R13
906/m	13	4	1	5	3	1	4	9	6	R13
909/p	7	2	2	2	2	2	2	7	7	B7
909/m	6	2	2	2	3	2	4	2	8	C6
Normal										
902/p	7	2	2	4	2	2	2	7	8	NA
902/m	13	2	1	3	1	2	2	9	8	NA
903/p	6	2	2	2	3	2	4	6	4	NA
903/m	10	5	1	4	2	1	1	6	3	NA
904/p	7	2	1	3	1	2	1	3	8	NA
908/p	9	4	1	5	2	1	4	6	3	NA
908/m	5	5	1	4	3	2	2	3	8	NA
910/p	9	2	1	3	3	2	3	7	7	NA
910/m	8	1	2	2	3	2	1	5	8	NA
911/p	7	4	1	5	2	1	4	7	2	NA
911/m	5	6	1	4	1	2	2	6	4	NA
907/p	11	5	1	4	3	2	2	7	6	NA
907/m	5	1	2	2	2	2	7	3	9	NA
905/p	13	2	1	3	1	2	2	7	8	NA
905/m	13	2	2	2	2	2	1	1	10	NA
906/p	6	2	2	2	3	2	4	6	6	NA
906/m	7	4	1		2	1	4	7	6	NA
909/p	7	5	1	4	3	2	5	6	6	NA
909/m	8	6	1	3	2	1	1	6	5	NA

* Polymorphisms tested are arranged 9qtel–9qcen. p, paternal; m, maternal haplotype. Core haplotypes as in Sirugo et al. [1992]. NA, not applicable.

TABLE III. Identity of Haplotypes in FRDA Region for Acadian Ataxia Families 909 and 903*

Family	909	909	909	909	909	909	909	903	903	903
Individual (see Fig. 2)	I-1	III-2	III-3	III-4	III-5	III-6	III-7	II-2	II-1	III-1	III-2	II-2
Affection status	Normal	Ataxia	Ataxia	Ataxia	Normal	Normal	Normal	Normal	Normal	Ataxia	Normal	Normal
Markers												
GS4	77	76	76	76	78	67	78	68	66	76	61	71
MCT-MS	25	22	22	22	56	25	56	26	22	22	25	25
MCT-*Msp*I	21	22	22	22	11	21	11	21	22	22	21	21
GS2	24	22	22	22	–	–	–	23	22	22	24	24
26P	23	23	23	23	32	33	32	32	33	23	32	22
DR47	22	22	22	22	21	22	21	21	22	22	21	21
FR1	25	24	24	24	51	45	51	41	44	24	41	21
FR2	24	28	28	28	47	84	47	87	88	28	84	24
A3U1	12	11	11	11	22	12	22	12	21	11	12	12
FR71A	21	–	22	22	11	21	11	21	12	22	21	21
F5225	23	23	23	23	31	33	31	31	13	23	34	24
FR8	55	58	58	58	55	85	55	85	48	58	85	55
FR7	76	72	72	72	66	26	–	26	62	72	26	76
FR5	76	78	78	78	65	86	65	85	48	78	83	73

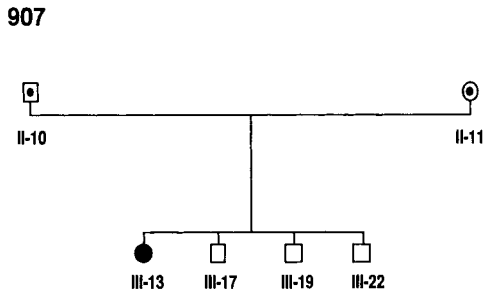
* –, untyped individual.

Recombination Event in an Unaffected Sib in Family 907

In Figure 4 we present detailed typing for the FRDA region on selected sibs of proposita III-13 in Figure 1. In unaffected individual III-22 we detected the presence of a maternal recombination between the disease and the linked markers. In addition to the sibs shown in Figure 4, we have detailed typings on 9 others in this family. No other inconsistencies were seen. This recombination event thus excludes the FRDA gene from the centromeric side of CS2.

DISCUSSION

Our study of autosomal-recessive ataxia in the Acadian population of New Brunswick in Eastern Canada demonstrated clinically distinct forms of the disease. FRDA-Acad also occurs in the Louisiana Acadian population. We showed linkage of FRDA-Acad to the FRDA region on chromosome 9. The D9S15–D9S5 core haplotype C6 is shared by New Brunswick and Louisiana Acadians, reinforcing the clinical identity of Friedreich ataxia in the two populations. Our results show conservation of the C6 FRDA-Acad haplotype through 8–10 generations, since the divergence of the populations from their common roots in Atlantic Canada.



#	II-10	III-13	III-17	III-19	III-22	II-11
GS4	6,11	6,9	11,5	6,5	6,5	9,5
MCT-MS	2,5	2,2	5,1	2,1	2,1	2,1
MCT-MspI	2,1	2,2	1,2	2,2	2,2	2,2
GS2	2,4	2,2	4,2	2,2	2,2	2,2
26P	3,3	3,2	3,2	3,2	3,2	2,2
DR47	2,2	2,2	2,2	2,2	2,2	2,2
FD1	nt	nt	nt	nt	nt	nt
FR1	4,2	4,2	nt	4,7	4,7	2,7
FD2	nt	nt	nt	nt	nt	nt
FR2	8,3	8,8	3,11	8,11	8,11	7,11
FR6	nt	nt	nt	nt	nt	nt
A3U1	1,2	1,1	2,2	1,2	1,2	1,2
FR71A	2,1	2,2	1,1	2,1	2,1	2,1
CS2	2,2	2,1	2,2	2,2	2,1	1,2
CD1	2,2	2,1	2,2	2,2	2,1	1,2
FR8	8,3	8,9	3,8	8,8	8,9	9,8
FR7	2,7	2,6	nt	2,3	2,6	6,3
FR5	8,6	8,7	nt	8,9	8,7	7,9

Fig. 4. Recombination between FRDA and linked markers in family 907, placing the gene telomeric of CS2. Results of typings on only one each of the affected, gene carrier, and normal sibs of individual III-22, of family 907, are presented. Order of polymorphisms tested is from telomere to centromere on 9q [Rodius et al., 1994]. Extent of maternal recombination event in III-22 is shown.

The second important FRDA-Acad haplotype (B7) also occurs in classical FRDA in Quebec. The documented settlement of French-Canadians from Lower Canada (the present day Province of Quebec) into areas of New Brunswick resettled by Acadians in the late eighteenth century may explain this observation. Using published genealogic records of the region [Arsenault, 1978], we traced back family names that may distinguish the origins of the ataxia chromosomes segregating in the families. In families 903, 909, and 910, we found common Quebec family names. Their inheritance correlated with the apparent origins of the B7 haplotype (data not shown). Due to the lack of complete genealogies, we found no Quebec patronyms associated with the B7 haplotypes in family 908.

Minor ataxia-associated haplotypes may reflect the recorded settlement of immigrants into the area from Ireland, France, and Scotland after the establishment of Acadians in Louisiana.

Based on clinical criteria, our families can be divided into two groups. A homogeneous clinical picture, compatible with FRDA-Acad emerges for families 902–904, 908, 910, and 911. Different FRDA-linked haplotypes have no apparent bearing on clinical manifestations.

In the second group, composed of families 905–907 and 909, we identified a disease variant, Acadian spastic ataxia (SPA-Acad). This variant is clinically distinct from other known autosomal-recessive spastic ataxias, including Charlevoix-Saguenay ataxia [Bouchard et al., 1978], and it is linked to the FRDA region on chromosome 9q.

In family 906, SPA-Acad is associated with unique haplotype R13. This family is part of the extended kindred (families 905–907) (Fig. 1) where both FRDA-Acad and SPA-Acad segregate. The combination of FRDA-Acad haplotype C6 with SPA-Acad haplotype R13 in family 905 has the clinical manifestations of FRDA-Acad. The affected individuals in family 907 have inherited haplotype C6 from the paternal side and B9 from the maternal side, respectively. If the three haplotypes revealed different mutations at the FRDA locus, we would expect to find the affected individuals from family 906 to be homozygotes for a SPA-Acad mutation, and the affected individual in family 905 to be a compound heterozygote for the mutations associated with haplotypes R13 and C6. The expected intermediate clinical picture between FRDA-Acad and SPA-Acad was not observed. Instead, the affected individual in family 905 had typical FRDA-Acad, as if the paternal FRDA-Acad-bearing chromosome C6 exerted a dominant effect on the R13 SPA-Acad chromosome.

In family 909 the combination of haplotypes B7 and C6 resulted in SPA-Acad. The same haplotypes, but with reversed parental origin, are associated with FRDA-Acad in the affected individual in family 903. The presence of clinically different manifestations associated with the same combination of FRDA haplotypes may reflect the action of modifiers rather than different mutations on the same haplotypes. However, the parental origin of the haplotypes may play an unidentified role in the expression of the phenotype. The clinical manifestations of FRDA-Acad rather than SPA-Acad in family 905 may also reflect the paternal origin of the C6 haplotype. Such rare observations (one affected individual each in families 903 and 905, and 3 in family 909) may prompt others to correlate clinical findings and haplotype origins on other populations with distinct forms of FRDA and haplotype conservation. The biological reason for clinically distinct conditions associated with the same haplotypes may be understood once the FRDA gene product is known and the causal mutations have been identified.

The recombination event in family 907 places the FRDA gene telomeric to CS2 and excludes most of the coding regions of candidate gene STM-7 [Carvajal et al., 1995]. In addition, two independent recombination events observed in classical FRDA families from Quebec confined the gene to the 450-kbp interval between D9S411E–CS2 (Richter et al., in preparation). Our current results substantiate the localization of the FRDA gene to this interval, based on a recombination event observed in patients homozygous by descent [Monros et al., 1994]. The loss of homozygosity in a consanguineous Tunisian family has excluded the region between D9S411E–D9S202 [Rodius et al., 1994]. The absence of mutations in candidate gene X104 has effectively excluded the region between D9S202–FR2 from containing the FRDA gene [Duclos et al., 1994]. Reexamination of the family investigated by Monros et al. [1994] with new markers F8101, F5225, F71, and FR6 showed loss of homozygosity in the propositus at marker F8101, while homozygosity was maintained at more telomeric markers [Montermini et al., 1995]. Thus, the most likely candidate region for the FRDA gene is a 150-kbp interval between FR2–F8101.

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